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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,749	08/12/2002	Constance E Brinckerhoff	DC-0155	2413

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,749	BRINCKERHOFF ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 21, 2004. Currently, claims 1-5 are pending. Claims 3-5 have been withdrawn as drawn to non-elected subject matter.

1. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn. This action contains new grounds of rejection necessitated by amendment.

Priority

2. This application is a 371 application of PCT/US99/26610, filed November 10, 1999 and priority to provisional application 60/110,266, filed November 30, 1998.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Response to Arguments

As provided in the March 1, 2003 O.G. Notice: "an incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See 35 U.S.C. 132(a). If an incorporation-by-reference statement is included in an amendment to the specification

to add a benefit claim after the filing date of the application, the amendment would not be proper. When a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference statement of the prior application. See Dart Industries v. Banner, 636 F.2d 6 4, 207 USPQ 273 (C.A.D.C. 190).

The instant amendments to the specification are therefore objected to as new matter because the incorporation by reference is inappropriate.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-2 are drawn to a method of diagnosing a matrix metalloproteinase-1 related cancer in a patient comprising detecting in the patient a AAGAT to AAGGAT polymorphism in the promoter sequence comprising SEQ ID NO: 6 and thereby diagnosing a MMP-1 related cancer in the patient.

The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art supports the unpredictability of the broadly drawn claims.

Also, the claims are directed to matrix metalloproteinase-1 related cancer.

Matsumura et al. (J. Cancer Res. Clin. Oncol., Vol. 130, pages 259-265, 2004) teaches that the frequency of 1G/2G genotypes in gastric cancer patients was similar to those in controls (p=0.57). The degree of tumor invasion, the presence of lymph node metastasis and clinical stage showed no significant association with the SNP. Matsumura teaches that the presence of 2G allele in the MMP-1 promoter did not enhance the risk of gastric cancer, however it may be involved in differentiation of gastric cancer.

Przybylowska et al. (Experimental Oncology, Vol. 24, pages 25-27, March 2002) teaches analyzing a guanine insertion/deletion polymorphism (the 1G/2G polymorphism) within the promoter region of MMP-1 gene. Przybylowska teaches no differences between genotypes of the 1G/2G polymorphism in cancer tissue and distant

mucosa was found. The distributions of the genotypes in cancer patients and control did not differ significantly ($p>0.05$). Przbylowska teaches that the 1G/2G polymorphism may not be associated with colorectal cancer.

Wenham et al. (J. of Soc. Gynecologic Investigation, Vol 10, No. 6, pages 381-387, September 2003) teaches the 2G allele frequency did not differ significantly between ovarian cancer patients and controls. Wenham teaches that "the reported association between the MMP1 promoter polymorphism and ovarian cancer risk was not supported by our data."

Lai et al. (Gynecologic Oncology, Vol. 96, pages 314-319, 2005) teaches the MMP-1 polymorphism was assessed in high-grad squamous intraepithelial lesions (HSILs) and 197 invasive squamous cell carcinomas (SCCs). The genetic polymorphisms of the MMP-1 are not associated with the risk of HSIL and SCC.

Ju et al. (Cancer letters, Vol. 217, pages 191-196, 2005) teaches analysis of promoter polymorphism in the matrix metalloproteinase-1 and risk of cervical cancer in Korean women. Ju teaches that Koreans with specific polymorphisms in MMP-1 are neither more susceptible to develop cervical cancer nor more vulnerable for cancer progression.

The art teaches analysis of many diseases and a single nucleotide polymorphism in the promoter of the matrix-metalloproteinase-1 gene. Lee et al. (Scand J. Rheumatol. Vol. 32, pages 235-239, 2003) teaches the genotype distribution of the MMP-1 promoter did not differ between rheumatoid arthritis patients and control subjects. The promoter polymorphism in the MMP-1 promoter may not play an important role in the susceptibility of RA, but the polymorphism may be related to clinical phenotypes. Lee further suggests that there may be ethnic differences in polymorphisms. Lee compared

their data with the published data on Caucasians and noticed significant difference in MMP-1 polymorphisms between Caucasians and Koreans (page 238, col. 1).

Moreover, the specification teaches that analysis of the 1G/2G polymorphism was examined in 100 controls and several tumor cell lines. The prior art establishes that cell lines are not appropriate means for examining associations with diseases. Specifically, Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease."

More specifically, Sidransky et al. (US Pat. 5,856,094, January 1999) teaches a comparison between cell lines and primary tumors. In the case of p16, the rate of homozygous deletions ranged from 40-60% of breast cancer cell lines, however, neither homozygous deletions or point mutations are typically observed in primary breast carcinomas (col. 2, lines 10-15). Therefore, presence of homozygous deletions in cell lines is not indicative of primary tumors.

Moreover, Teng et al. (US Pat. 5,989,885, November 1999) teaches that discovery of mutations in cancer cell lines requires determination of whether the lesions occur in primary or metastatic tumors (col. 39, lines 49-55). Despite detection of mutation in cancer cell lines, no sequence variants were detected in 45 primary breast tumor specimens (col. 39, lines 53-56). Teng states that the MKK4r mutations in these lines were possibly generated wile these cells were cultured in vitro (col. 40, lines 5-10).

Guidance in the Specification.

The specification teaches that MMP-1 promoter DNA may contain 1 G at position –1607 or 2 Gs at that location. The full length DNA sequence of MMP-1 with only 1 G at position –1607 is depicted in SEQ ID NO: 3. As discussed above, the disclosure of –1607 does not clarify the location of the polymorphism analyzed in the specification. A review of SEQ ID NO: 3 revealed numerous sequences where this polymorphism may occur. The specification fails to provide the background for this polymorphism. A quick search of SEQ ID NO: 3 reveals there are approximately 8 sites of AAGAT which would enable an Ets transcription factor binding site (positions 540; 1030; 1930; 2760; 2790; 2820; 3170 and 3260). The specification does not appear to provide any guidance as to which of these sites is analyzed. Applicants are reminded that no new matter may be entered into the claims.

The specification provides an analysis of this 1G/2G difference in the leukocyte clone sequence and the A2058 melanoma sequence (page 8). 100 control DNAs derived from CEPH pedigrees and several tumor cell lines were analyzed. The occurrence of 2G homozygotes in the CEPH controls was determined to be approximately 30%. In the tumor cell lines, it was 62.5% ($p<0.0001$)(page 8).

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses

Working Examples

The specification has no working examples of sampling of patients with matrix metalloproteinase-1 related cancers to determine frequencies in the populations.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied before the skilled artisan could use the claimed invention as broadly as claimed.

The claims are broadly drawn to diagnosing a MMP-1 related cancer. The specification contemplates cancer. The post-filing date art makes it clear that some cancers are associated with MMP-1 and some cancers are not associated with MMP-1 promoter 2G polymorphism. For example, the art teaches that in colorectal cancer, ovarian cancer, high-grad squamous intraepithelial lesions and invasive squamous cell carcinomas, and cervical cancer, no association between the polymorphism and the cancer was detected. Thus, it is unpredictable which cancers in which populations and under which conditions are associated with the promoter polymorphism. The skilled artisan would be required to perform additional experimentation for each of the MMP-1 cancers in the ethnic populations to determine whether an association is present prior to using the claimed method. Since some cancers are and some cancers are not associated with the polymorphism, it is unpredictable which cancers are associated with the polymorphisms without further unpredictable and undue experimentation. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The analysis provided in the specification is directed at 100 controls and tumor cells lines. As discussed above, tumor cell lines are not representative of tumors from patients. Given the teachings in the specification and the art, there is no correlation that may be accurately inferred between cell lines and patients tumors.

Moreover, the art and the specification teaches that the 2G polymorphism is present in frequencies of about 30%. Thus, based upon the claim language, the skilled artisan would incorrectly diagnose a patient with a MMP-1 disease 30% of the time. In the cases where an association exists, the art appears to be directed to an increased predisposition, but the art fails to teach a diagnostic based upon the presence of a single nucleotide polymorphism.

Further, Lee specifically points out that there is an ethnic difference in the 2G/1G polymorphism. Lee compared the data with the published data on Caucasians and noticed a significant difference in MMP-1 polymorphisms between Caucasians and Koreans (pages 238, col. 1). The genotype distribution of the MMP-1 promoter differed significantly between Caucasian and Korean control subjects (p=0.00038)(pages 238, col. 1). Therefore, it is clear that an association determined in a single population would not be indicative of an association in all populations. The skilled artisan would be required to perform additional experimentation to determine whether the disease and the polymorphism is associated. As evidenced by the art, it is unpredictable that any polymorphism is associated with any particular disease in any particular population.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches a lack of association between a polymorphisms and numerous MMP-1 cancers, the lack of specific guidance as to which MMP-1 polymorphism is analyzed, the ethnic differences and the broad inclusion of any patient, and diagnostics. Further,

the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that based upon the high level of appreciation in the art concerning the association between MMP-1 expression and cancer diagnostics, the claims are enabling. This arguments has been thoroughly considered but is not convincing because the art teaches that an association between cancers and the promoter polymorphism were not correlative. The art teaches that in colorectal cancer, ovarian cancer, high-grade squamous intraepithelial lesions and invasive squamous cell carcinomas, and cervical cancer, no association between the polymorphism and the cancer was detected. Thus, it is unpredictable which cancers in which populations and under which conditions are associated with the promoter polymorphism. In order to practice the claimed invention as broadly as claimed, the skilled artisan would be required to perform additional, undue and unpredictable experimentation to determine which cancers are associated with the polymorphism and in which populations. While the art may have appreciated an association between MMP-1 expression and cancer, the art further illustrates that when associations were

analyzed to confirm an association between the polymorphism and the cancers generically, no associations could be made in many studies. The response relies on a very specific teaching of Matsumura to support the predictability. The response states that there is a difference between diffuse and intestinal type gastric cancer. While this one type of gastric cancer may be associated with the polymorphism, this single type of a larger group of gastric cancer when taken in light of the teachings in the art as a whole, does not appear to overcome the showing of unpredictability in the art as to whether or not the polymorphism is associated with cancers.

The response asserts that enablement varies inversely with the degree of predictability. This argument has been considered and the examiner agrees with this analysis. In the instant situation it is clear that there is little predictability about wether cancers are associated over ethnic populations in each of the sexes. The art teaches numerous instances where cancers are not predictably associated with the polymorphism, where ethnic differences play a role in the association and where gender plays a role in association. Thus, the large degree of unpredictability would weigh in favor of a larger degree of enablement from the specification.

The working examples in the specification relied upon by the response on page 11 are directed to cell lines. The response provides a single example that the expression of human tissue inhibitor of metalloproteinases 1 and 2 is the same in vivo and in cell culture. This argument has been considered, but not found persuasive. As discussed above, at great length, cell lines are not representative of tumors in patients. The art discusses numerous deficiencies in relying upon cell lines. Since the art

teaches both the ability and the inability to use cell lines, it is unpredictable whether cell lines may be reliably used for analyzing polymorphisms as indicative of diseases. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-2 are indefinite because it is unclear whether the claims are drawn to detecting SEQ ID NO: 6 as indicative of the mutation or whether the claim is drawn to a SEQ ID NO: 6 as the promoter sequence. The phrasing of "comprising SEQ ID NO: 6" is unclear whether the mutation comprises SEQ ID NO: 6 or whether the promoter sequence comprises SEQ ID NO: 6. It is noted from the specification that SEQ ID NO: 6 does not comprise the insertion. SEQ ID NO: 7 comprises the insertion.

Conclusion

5. No claims allowable.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
March 16, 2005